EAST Search History

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	5870	"HMG-CoA reductase"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2006/08/31 11:04
L2	199958	virus	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2006/08/31 11:04
L3	45145	"viral infection"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2006/08/31 11:04
L4	557	L1 and L3	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2006/08/31 11:16
L5	1306	L1 and L2	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2006/08/31 11:17
L6	8668	lovastatin or simvastatin or fluvastatin or atorvastatin or pravastatin or mevastatin	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2006/08/31 11:18
L7	1051	L3 and L6	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2006/08/31 11:18
L8	6301	"respiratory syncytial virus"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2006/08/31 11:18
L9	6301	L8 and L8	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2006/08/31 11:18

EAST Search History

L10	87	L7 and L8	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2006/08/31 11:46
L11	3	"9958505"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2006/08/31 11:49
L12	9	"9639144"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2006/08/31 11:49

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NEWS 9	MAY 30	The F-Term thesaurus is now available in CA/CAplus
NEWS 10	JUN 02	The first reclassification of IPC codes now complete in INPADOC
NEWS 11	JUN 26	TULSA/TULSA2 reloaded and enhanced with new search and and display fields
NEWS 12	JUN 28	Price changes in full-text patent databases EPFULL and PCTFULL
NEWS 13	JUl 11	CHEMSAFE reloaded and enhanced
NEWS 14	JUl 14	FSTA enhanced with Japanese patents
NEWS 15	JUl 19	Coverage of Research Disclosure reinstated in DWPI
NEWS 16	AUG 09	INSPEC enhanced with 1898-1968 archive
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NEWS 18	AUG 30	CA(SM)/CAplus(SM) Austrian patent law changes

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=> s HMG CoA reductase
L1       25258 HMG COA REDUCTASE

=> s virus or viral
L2     2254859 VIRUS OR VIRAL

=> s L1 and L2
L3         349 L1 AND L2

=> dup rem L3
PROCESSING COMPLETED FOR L3
L4          245 DUP REM L3 (104 DUPLICATES REMOVED)

=> s L4 and (AY<2002 or PY<2002 or PRY<2002)
'2002' NOT A VALID FIELD CODE
'2002' NOT A VALID FIELD CODE
   2 FILES SEARCHED...
'2002' NOT A VALID FIELD CODE
'2002' NOT A VALID FIELD CODE
'2002' NOT A VALID FIELD CODE
'2002' NOT A VALID FIELD CODE
L5          87 L4 AND (AY<2002 OR PY<2002 OR PRY<2002)

=> s respiratory syncytial virus
L6       22638 RESPIRATORY SYNCYTIAL VIRUS

=> s L5 and L6
L7           4 L5 AND L6

=> d 1-4 ibib abs

L7   ANSWER 1 OF 4  CAPLUS  COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:         2002:755195  CAPLUS <<LOGINID::20060831>>
DOCUMENT NUMBER:          137:273169
TITLE:                    Method of inhibiting viral infection using
                          HMG-CoA reductase
                          inhibitors and isoprenylation inhibitors
INVENTOR(S):              Graham, Barney Scott; Gower, Tara L.; Pastey, Manoj K.
PATENT ASSIGNEE(S):       USA
SOURCE:                   U.S. Pat. Appl. Publ., 24 pp.
                          CODEN: USXXCO
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.           KIND   DATE        APPLICATION NO.          DATE
     ---------------      ----   --------    --------------------     --------
     US 2002142940         A1    20021003    US 2001-981682           20011016 <--
PRIORITY APPLN. INFO.:                       US 2000-241247P      P   20001017 <--
AB   Applicants provide methods of inhibiting viral infections, and
     treating an infected individual with AIDS, respiratory
     syncytial virus infection, parainfluenza virus
     infection, and other viral infections.  Inhibitors of Rho
     isoprenylation are used to inhibit Rho cell surface attachment, thereby
     inhibiting the use, by viruses, of Rho as a receptor for
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infection of susceptible cells. Isoprenylation inhibitors include inhibitors specific for the enzymes farnesyltransferase and geranylgeranyltranferase, as well as inhibitors of general cholesterol biosynthesis, such as HMG-CoA reductase inhibitors. Mice were treated with 1 mg/day lovastatin, 50 mg/day gemfibrozil, or PBS by oral gavage beginning three days prior to infection with either RSV or vaccinia virus. Vaccinia replication and illness was not effected by lovastatin or gemfibrozil treatment compared to PBS treated controls. Gemfibrozil and PBS treated mice infected with RSV had a peak titer in the lung of 6.5+/-0.43 (log10 pfu/gm) and 6.5+/-0.19 (log10 pfu/gm), resp., while RSV replication in lovastatin treated mice was reduced by nearly 100-fold to 4.7+/-0.4 (log10 pfu/gm).

L7 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:321371 CAPLUS <<LOGINID::20060831>>
DOCUMENT NUMBER: 135:150874
TITLE: RhoA Is Activated During Respiratory Syncytial Virus Infection
AUTHOR(S): Gower, Tara L.; Peeples, Mark E.; Collins, Peter L.; Graham, Barney S.
CORPORATE SOURCE: Department of Microbiology and Immunology, Vanderbilt University School of Medicine, Nashville, TN, 37232, USA
SOURCE: Virology (2001), 283(2), 188-196
CODEN: VIRLAX; ISSN: 0042-6822
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Respiratory syncytial virus (RSV) is an important human pathogen that can cause severe and life-threatening respiratory infections in infants and immunocompromised adults. The authors have recently shown the RSV F glycoprotein, which mediates viral fusion and entry, interacts with the cellular protein RhoA in two-hybrid and in vitro binding assays. Whether this interaction occurs in living cells remains an open question. However, because RhoA signaling is associated with many cellular functions relevant to RSV pathogenesis such as actin cytoskeleton organization, expression of proinflammatory cytokines, and smooth muscle contraction, the authors asked whether RhoA activation occurred during RSV infection of HEp-2 cells. They found that the amount of isoprenylated and membrane-bound RhoA in RSV-infected cultures was increased. Further evidence of RhoA activation was demonstrated by downstream signaling activity mediated by RhoA. There was an increase in p130cas phosphorylation during RSV infection, which was prevented by Y-27632, a specific inhibitor of Rho kinase, or lovastatin, an HMG-CoA reductase inhibitor that reduces the synthesis of groups needed for isoprenylation. In addition, RSV infection of HEp-2 cells resulted in an increase in the formation of actin stress fibers. Pretreatment of HEp-2 cells with Clostridium botulinum C3 exotoxin, an enzyme that specifically ADP-ribosylates and inactivates RhoA, prevented RSV-induced stress fiber formation. Thus, RhoA and subsequent downstream signaling events are activated during RSV infection, which has implications for RSV pathogenesis. (c) 2001 Academic Press.
REFERENCE COUNT: 54 THERE ARE 54 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1997:121345 CAPLUS <<LOGINID::20060831>>
DOCUMENT NUMBER: 126:126927
TITLE: Stable copper(I) complexes as active therapeutic substances
INVENTOR(S): Pallenberg, Alexander J.; Branca, Andrew; Marschner, Thomas M.; Patt, Leonard M.
PATENT ASSIGNEE(S): Procyte Corporation, USA; Pallenberg, Alexander J.;

Branca, Andrew; Marschner, Thomas M.; Patt, Leonard M.
SOURCE: PCT Int. Appl., 104 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9639144	A1	19961212	WO 1996-US10122	19960606 <--
W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA				
AU 9662748	A1	19961224	AU 1996-62748	19960606 <--
PRIORITY APPLN. INFO.:			US 1995-468645 A	19950606 <--
			WO 1996-US10122 W	19960606 <--

AB Stable Copper(I) complexes and methods relating thereto are disclosed. The stable Copper (I) complexes comprise a Copper(I) ion complexed by a multi-dentate ligand which favors the +1 oxidation state for copper. The complexes may be used as wound healing agents, anti-oxidative agents, anti-inflammatory agents, lipid modulating agents, signal transduction modulating agents, hair growth agents, and antiviral agents. Uses of this invention also include inhibition of viral infection, as well as inhibiting transmission of sexually transmitted diseases. The stable Copper(I) complexes of the invention include neocuproine Copper(I) and bathocuproine disulfonic acid Copper(I). Preparation of copper (I) neocuproine is described, as are inhibitory effects of the complexes of the invention against e.g a variety of viruses.

L7 ANSWER 4 OF 4 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2001:194941 BIOSIS <<LOGINID::20060831>>
DOCUMENT NUMBER: PREV200100194941
TITLE: Antiviral activity of lovastatin against respiratory syncytial virus in vivo and in vitro.
AUTHOR(S): Gower, Tara L.; Graham, Barney S. [Reprint author]
CORPORATE SOURCE: Vanderbilt University School of Medicine, 1161 21st Ave. South, A-4103 MCN, Nashville, TN, 37232-2582, USA
bgraham@mail.nih.gov
SOURCE: Antimicrobial Agents and Chemotherapy, (April, 2001) Vol. 45, No. 4, pp. 1231-1237. print.
CODEN: AMACCQ. ISSN: 0066-4804.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 20 Apr 2001
Last Updated on STN: 18 Feb 2002

AB Respiratory syncytial virus (RSV) is an important human pathogen that can cause severe and life-threatening respiratory infections in infants and immunocompromised adults. We have recently shown that the RSV F glycoprotein, which mediates viral fusion, binds to RhoA. One of the steps in RhoA activation involves isoprenylation at the carboxy terminus of the protein by geranylgeranyltransferase. This modification allows RhoA to be attached to phosphatidyl serine on the inner leaflet of the plasma membrane. Treatment of mice with lovastatin, a drug that inhibits prenylation pathways in the cell by directly inhibiting hydroxymethylglutaryl coenzyme A reductase, diminishes RSV but not vaccinia virus replication when administered up to 24 h after RSV infection and decreases virus-induced weight loss and illness in mice. The inhibition of replication is not likely due to the inhibition of cholesterol

biosynthesis, since gemfibrozil, another cholesterol-lowering agent, did not affect virus replication and serum cholesterol levels were not significantly lowered by lovastatin within the time frame of the experiment. Lovastatin also reduces cell-to-cell fusion in cell culture and eliminates RSV replication in HEp-2 cells. These data indicate that lovastatin, more specific isoprenylation inhibitors, or other pharmacological approaches for preventing RhoA membrane localization should be considered for evaluation as a preventive antiviral therapy for selected groups of patients at high risk for severe RSV disease, such as the institutionalized elderly and bone marrow or lung transplant recipients.

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=> s lovastatin or simvastatin or fluvastatin or atorvastatin or pravastatin or
mevastatin
L8       48019 LOVASTATIN OR SIMVASTATIN OR FLUVASTATIN OR ATORVASTATIN OR
               PRAVASTATIN OR MEVASTATIN

=> s L4 and L8
L9         125 L4 AND L8

=> s L9 and (AY<2001 or PY<2001 or PRY<2001)
'2001' NOT A VALID FIELD CODE
'2001' NOT A VALID FIELD CODE
   2 FILES SEARCHED...
'2001' NOT A VALID FIELD CODE
'2001' NOT A VALID FIELD CODE
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'2001' NOT A VALID FIELD CODE
L10         19 L9 AND (AY<2001 OR PY<2001 OR PRY<2001)

=> d 1-19 L10 ibib abs

L10  ANSWER 1 OF 19  CAPLUS  COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:         2003:717608  CAPLUS <<LOGINID::20060831>>
DOCUMENT NUMBER:          139:224451
TITLE:                    Regulation of a post-ER pre-secretory proteolysis
                          (PERPP) pathway for apoB for drug screening and
                          treatment and diagnosis of cardiovascular and
                          metabolic disorders
INVENTOR(S):              Fisher, Edward; Williams, Kevin Jon
PATENT ASSIGNEE(S):       USA
SOURCE:                   U.S. Pat. Appl. Publ., 37 pp., Cont.-in-part of U.S.
                          Ser. No. 697,827, abandoned.
                          CODEN: USXXCO
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   2
PATENT INFORMATION:

     PATENT NO.           KIND   DATE        APPLICATION NO.          DATE
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     US 2003170643         A1    20030911    US 2002-100823           20020318 <--
     WO 2004014359         A1    20040219    WO 2002-US8487           20020318
         RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL,
             PT, SE, TR
PRIORITY APPLN. INFO.:                       US 1999-161537P      P  19991026 <--
                                             US 2000-697827       B2 20001026 <--
                                             US 2001-276557P      P  20010316
                                             US 2001-333053P      P  20011114
                                             US 2002-100823       A  20020318
AB   The present invention discloses a third degradation pathway for aopB in
     hepatic cells, in which the degradative process occurs between the other
     two, i.e., after lipidation in the endoplasmic reticulum (ER), but before
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export across the plasma membrane. It is named post-ER pre-secretory proteolysis (PERPP). PERPP can be triggered by Ω-3 fatty acids, also known as fish oils. PERPP does not act via microsomal lipid transfer protein inhibition, active proteosomes, cell-surface LDL receptors, cell-surface heparan sulfate proteoglycans, or functioning lysosomes. Phosphoinositide 3-kinase (PI-3 kinase) activation and lipid peroxidn. are involved. It is, therefore, an objective of the present invention to provide a novel method of treating cardiovascular or metabolic disorders or syndromes using a compound that stimulates PERPP, as well as a method of screening for drugs that stimulate PERPP to treat such disorders or syndromes. It is also an objective of the present invention to provide a method of screening for genes for diagnosing cardiovascular or metabolic disorders or syndromes associated with defects in PERPP. It is further an objective of the present invention to provide a method of treating HIV-infected patients and a method of screening for HIV protease inhibitors.

L10 ANSWER 2 OF 19 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:778718 CAPLUS <<LOGINID::20060831>>
DOCUMENT NUMBER: 137:289046
TITLE: Methods and compositions for enhancing pharmaceutical treatments
INVENTOR(S): Newman, Michael J.; Dixon, William Ross
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 47 pp., Cont.-in-part of U.S. Ser. No. 684,293.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 2002147197	A1	20021010	US 2002-104549		20020320 <--
PRIORITY APPLN. INFO.:			US 1999-158322P	P	19991008 <--
			US 2000-684293	A2	20001006 <--

OTHER SOURCE(S): MARPAT 137:289046
AB Improved methods are provided for therapeutic and/or preventative treatment to a mammal in which the mammal is protected against the toxicity of active pharmaceutical agents that (i) bind to or are substrates for P-gp, (ii) are taxane analogs, and/or (iii) are inhibitors of tubulin disassembly. Addnl. provided are compns. and methods useful for treating cell proliferative disorders. Further provided are methods of increasing the bioavailability of therapeutic and/or preventative treatments in a mammal. Particular embodiments are directed to increasing such bioavailability across the blood-brain barrier.

L10 ANSWER 3 OF 19 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:755195 CAPLUS <<LOGINID::20060831>>
DOCUMENT NUMBER: 137:273169
TITLE: Method of inhibiting viral infection using HMG-CoA reductase inhibitors and isoprenylation inhibitors
INVENTOR(S): Graham, Barney Scott; Gower, Tara L.; Pastey, Manoj K.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 24 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

US 2002142940	A1	20021003	US 2001-981682	20011016 <--
PRIORITY APPLN. INFO.:			US 2000-241247P P	20001017 <--

AB Applicants provide methods of inhibiting viral infections, and treating an infected individual with AIDS, respiratory syncytial virus infection, parainfluenza virus infection, and other viral infections. Inhibitors of Rho isoprenylation are used to inhibit Rho cell surface attachment, thereby inhibiting the use, by viruses, of Rho as a receptor for infection of susceptible cells. Isoprenylation inhibitors include inhibitors specific for the enzymes farnesyltransferase and geranylgeranyltranferase, as well as inhibitors of general cholesterol biosynthesis, such as HMG-CoA reductase inhibitors. Mice were treated with 1 mg/day lovastatin, 50 mg/day gemfibrozil, or PBS by oral gavage beginning three days prior to infection with either RSV or vaccinia virus. Vaccinia replication and illness was not effected by lovastatin or gemfibrozil treatment compared to PBS treated controls. Gemfibrozil and PBS treated mice infected with RSV had a peak titer in the lung of 6.5+/-0.43 (log10 pfu/gm) and 6.5+/-0.19 (log10 pfu/gm), resp., while RSV replication in lovastatin treated mice was reduced by nearly 100-fold to 4.7+/-0.4 (log10 pfu/gm).

L10 ANSWER 4 OF 19 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2000:716984 CAPLUS <<LOGINID::20060831>>
DOCUMENT NUMBER: 134:261122
TITLE: Safety and efficacy of HMG-CoA reductase inhibitors for treatment of hyperlipidemia in patients with HIV infection
AUTHOR(S): Penzak, Scott R.; Chuck, Susan K.; Stajich, Gregory V.
CORPORATE SOURCE: Southern School of Pharmacy, Department of Pharmacy Practice, Mercer University, Atlanta, GA, 30341-4155, USA
SOURCE: Pharmacotherapy (2000), 20(9), 1066-1071
CODEN: PHPYDQ; ISSN: 0277-0008
PUBLISHER: Pharmacotherapy Publications
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Study Objective: To assess the efficacy and safety of HMG-CoA reductase inhibitors (statins) in patients with human immunodeficiency virus (HIV) infection and hyperlipidemia. Design; Retrospective anal. Setting: HIV clinic. Patients: Twenty-six HIV-infected patients with hyperlipidemia. Intervention: Five patients received pravastatin, 13 lovastatin, 10 simvastatin, and 2 atorvastatin (total 30 courses). Measurements and Main Results: Redns. in cholesterol and triglycerides were used to assess efficacy; creatine kinase (CK), liver enzymes, and myalgia were markers of statin toxicity. After a median of 8.2 and 7.2 mo of treatment, the agents collectively reduced median baseline total cholesterol 27% (354 to 263 mg/dL) and triglycerides 15% (513 to 438 mg/dL), resp. Two patients, one with marked CK elevations, experienced myalgias with lovastatin, and two experienced transaminase elevations 3 or more times the upper limit of normal. Conclusion: Statins are effective in reducing total cholesterol and triglycerides in HIV-infected patients, although lipid levels infrequently return to normal. Lovastatin should be avoided in patients receiving concomitant drugs that may potentiate skeletal muscle toxicity with this agent.

REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 5 OF 19 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1999:736664 CAPLUS <<LOGINID::20060831>>
DOCUMENT NUMBER: 131:346502
TITLE: Combinations of protein farnesyltransferase inhibitors

and HMG-CoA reductase
inhibitors and their use to treat cancer and other diseases
INVENTOR(S): Leopold, Judith; Newton, Roger Schofield
PATENT ASSIGNEE(S): Warner-Lambert Company, USA
SOURCE: PCT Int. Appl., 66 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE	
WO 9958505	A2	19991118	WO 1999-US10188		19990510	<--
WO 9958505	A3	20000106				
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RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG						
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AU 9939792	A1	19991129	AU 1999-39792		19990510	<--
AU 758891	B2	20030403				
EP 1077949	A2	20010228	EP 1999-922898		19990510	<--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO						
BR 9911785	A	20010403	BR 1999-11785		19990510	<--
EE 200000660	A	20020415	EE 2000-660		19990510	<--
JP 2002514628	T2	20020521	JP 2000-548309		19990510	<--
NZ 508357	A	20020927	NZ 1999-508357		19990510	<--
US 6492410	B1	20021210	US 2000-674818		20001106	<--
ZA 2000006491	A	20020509	ZA 2000-6491		20001109	<--
NO 2000005680	A	20010110	NO 2000-5680		20001110	<--
HR 2000000771	A1	20010630	HR 2000-771		20001113	<--
BG 105003	A	20010731	BG 2000-105003		20001129	<--
HK 1038355	A1	20050429	HK 2001-109123		20011227	<--
PRIORITY APPLN. INFO.:			US 1998-85202P	P	19980512	<--
			US 1998-92253P	P	19980710	<--
			WO 1999-US10188	W	19990510	<--

OTHER SOURCE(S): MARPAT 131:346502
AB Novel combinations of inhibitors of protein farnesyltransferase enzymes and HMG CoA reductases enzymes are described, as well as methods for the preparation and pharmaceutical compns. of the same, which are useful in preventing or treating cancer, restenosis, psoriasis, endometriosis, atherosclerosis, or viral infections.

L10 ANSWER 6 OF 19 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1999:73929 CAPLUS <<LOGINID::20060831>>
DOCUMENT NUMBER: 130:262079
TITLE: Prenyltransferase inhibitors induce apoptosis in proliferating thyroid cells through a p53-independent, CrmA-sensitive, and caspase-3-like protease-dependent mechanism
AUTHOR(S): Vitale, Mario; Di Matola, Tiziana; Rossi, Guido; Laezza, Chiara; Fenzi, Gianfranco; Bifulco, Maurizio
CORPORATE SOURCE: Dipartimento di Biologia e Patologia Cellulare e Molecolare, Universita Federico II, Naples, 80131, Italy
SOURCE: Endocrinology (1999), 140(2), 698-704
CODEN: ENDOAO; ISSN: 0013-7227
PUBLISHER: Endocrine Society

DOCUMENT TYPE: Journal
LANGUAGE: English
AB The inhibitors of protein prenylation have been proposed for chemotherapy of tumors. Lovastatin, a 3-hydroxy-3-methylglutaryl-Co-enzyme A (HMG-CoA) reductase inhibitor, displays proapoptotic activity in tumor cells blocking the synthesis of isoprenoids compds. To test whether HMG-CoA reductase inhibition can induce apoptosis in proliferating thyroid cells, we studied the effects of lovastatin in normal and neoplastic thyroid cells and in primary cultures from normal human thyroids. In an immortalized human thyroid cell line (TAD-2) and in neoplastic cells, lovastatin induced cell rounding within 24 h of treatment. After 48 h the cells were detached from the plate and underwent apoptosis, as evidenced by DNA fragmentation. Morphol. changes and apoptosis did not occur in serum-starved quiescent TAD-2 cells or in primary cultures of normal thyrocytes. Mevalonate, the product of the HMG-CoA reductase enzymic activity, and the protein synthesis inhibitor cycloheximide completely blocked the effects of lovastatin in a dose-dependent fashion. The geranylgeranyl transferase GGTI-298 inhibitor mimicked the effects of lovastatin on cell morphol. and induced cell death, whereas the farnesyl transferase inhibitor FTI-277 was less effective to induce both cell rounding and apoptosis. Resistance to lovastatin-induced apoptosis by expression of the viral serpine CrmA and by the peptide inhibitor of caspases, Z-DEVD-fmk, demonstrated the involvement of CrmA-sensitive, caspase-3-like proteases. Inhibition of endogenous p53 activity did not affect the sensitivity of thyroid cells to lovastatin, demonstrating that this type of apoptosis is p53 independent. We conclude that lovastatin is a potent inducer of apoptosis in proliferating thyroid cells through inhibition of protein prenylation. This type of apoptosis requires protein synthesis, is CrmA sensitive and caspase-3-like protease dependent, and is independent from p53.
REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 7 OF 19 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1998:733606 CAPLUS <<LOGINID::20060831>>
DOCUMENT NUMBER: 130:104837
TITLE: Enhancement of the herpes simplex virus thymidine kinase/ganciclovir bystander effect and its antitumor efficacy in vivo by pharmacologic manipulation of gap junctions
AUTHOR(S): Touraine, Renaud L.; Vahanian, Nicholas; Ramsey, W. Jay; Blaese, R. Michael
CORPORATE SOURCE: Clinical Gene Therapy Branch, National Human Genome Research Institute, National Institutes of Health, Bethesda, MD, 20892, USA
SOURCE: Human Gene Therapy (1998), 9(16), 2385-2391
CODEN: HGTHE3; ISSN: 1043-0342
PUBLISHER: Mary Ann Liebert, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Apigenin, a flavanoid, and lovastatin, an HMG-CoA reductase inhibitor, upregulated gap junction (GJ) function and dye transfer in tumors expressing GJ and were inactive in the GJ-neg. tumor line N2a. N2a cells transfected with the connexin 43 gene showed restored cell-to-cell dye transfer, which could then be improved nearly fourfold by addition of apigenin. To test the drugs in HSV thymidine kinase/ganciclovir (HSV-tk/GCV) tumor killing, mixts. of 90% wild-type (WT) with 10% HSV-tk gene-modified MCA38 adenocarcinoma cells were exposed in vitro to GCV ± apigenin or lovastatin. A significant bystander effect (BSE) was seen following GCV treatment alone, while neither apigenin or lovastatin alone had any effect on the

recovery of viable tumor colonies. However, GCV-treated cultures also exposed to apigenin or lovastatin showed an increased BSE and reduced tumor cell recovery. Thirty percent of mice bearing tumors from the same mixture of 90% WT and 10% HSV-tk MCA38 cells treated with GCV alone became tumor free. Tumor-bearing mice given only two or three injections of lovastatin or apigenin during GCV treatment had a doubling of the antitumor response rate, with 60-70% of the mice achieving complete remission. These results support the hypothesis that the transfer of phosphorylated GCV from HSV-tk gene-expressing cells to neighboring WT tumor cells is a major component of the BSE and that pharmacol. manipulation of GJ function with lovastatin or apigenin can result in striking improvement in the antitumor response in mice with tumors modified to contain as few as 10% HSV-tk cells.

REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 8 OF 19 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1998:380126 CAPLUS <<LOGINID::20060831>>
DOCUMENT NUMBER: 129:104047
TITLE: Atherosclerosis in Marek's disease virus infected hypercholesterolemic roosters is reduced by HMGCoA reductase and ACE inhibitor therapy
AUTHOR(S): Lucas, Alexandra; Dai, Erbin; Liu, Li-Ying; Nation, Patric N.
CORPORATE SOURCE: Div. Cardiology, John P. Robarts Research Inst., Univ. Western Ontario, London, ON, N6A-5K8, Can.
SOURCE: Cardiovascular Research (1998), 38(1), 237-246
CODEN: CVREAU; ISSN: 0008-6363
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Accelerated atherosclerosis is associated with herpesviral infection both in transplant patients and after balloon angioplasty. Marek's disease virus (MDV) is a herpesvirus that induces accelerated atherosclerosis associated with the development of an invasive lymphoma in hyperlipemic roosters. We have examined the effects of pravastatin , a 3-hydroxy-3-methylglutaryl-CoA (HMG CoA) reductase inhibitor and quinapril, an angiotensin converting enzyme (ACE) inhibitor, on atherosclerosis development in MDV infected, cholesterol fed rooster chicks. The effects of these drugs on plaque growth after MDV infection were examined in two studies. In Study 1, MDV infected White Leghorn rooster chicks were divided into 4 groups assigned to normal or high cholesterol diet, and treated at three months of age with either pravastatin or saline. In Study 2, cholesterol fed rooster chicks infected with MDV were divided into 3 groups for treatment with either pravastatin, quinapril, or saline control. A significant decrease in plaque area was detected after 60 days of treatment with both pravastatin and quinapril in cholesterol fed chicks ($P < 0.001$). Lymphocyte infiltration into the arterial wall or target organs was not inhibited by treatment with either drug. (1) HMGCoA reductase inhibitor and ACE inhibitor therapy reduce atherosclerosis induced by virus infection and cholesterol diet, but this decrease in plaque growth is not due to a reduction in lymphocyte invasion. (2) MDV infection in cholesterol fed roosters provides a model for virus-induced arterial injury in atherogenesis.

REFERENCE COUNT: 53 THERE ARE 53 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 9 OF 19 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1995:494199 CAPLUS <<LOGINID::20060831>>
DOCUMENT NUMBER: 122:283768
TITLE: 3'-untranslated sequences mediate post-transcriptional regulation of 3-hydroxy-3-methylglutaryl-CoA reductase

mRNA by 25-hydroxycholesterol
AUTHOR(S): Choi, Jae Won; Peffley, Dennis M.
CORPORATE SOURCE: Dep. Pharmacol. Mol. Biol., Univ. Health Sciences/Chicago Med. Sch., North Chicago, IL, 60064, USA
SOURCE: Biochemical Journal (1995), 307(1), 233-8
CODEN: BIJOAK; ISSN: 0264-6021
PUBLISHER: Portland Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In an earlier study [Choi, Lundquist and Peffley (1993) Biochem. J. 296, 859-866], we determined that 25-hydroxycholesterol regulates 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase mRNA through a post-transcriptional mechanism that requires protein synthesis. To investigate whether 3'-untranslated sequences play a role in 25-hydroxycholesterol-mediated posttranscriptional control, we ligated approx. 1400 bp of the 3'-untranslated region of HMG-CoA reductase cDNA to the coding region of human β-globin DNA. β-Globin-3'-untranslated reductase fusion constructs were then transiently expressed in Chinese hamster ovary fibroblasts under conditions known to regulate reductase mRNA. There were no differences in β-globin RNA levels in transfected cells incubated with or without lovastatin, a competitive inhibitor of reductase. However, in the presence of lovastatin and an oxysterol, 25-hydroxycholesterol, β-globin RNA levels were decreased approx. 2-fold. Inhibition of protein synthesis with cycloheximide blocked the effects of 25-hydroxycholesterol on β-globin RNA. Moreover, replacing the 3'-untranslated sequences with 1367 bp of the simian virus 40 enhancer region eliminated the regulatory effect of 25-hydroxy-cholesterol. Because the fusion construct has no sterol regulatory elements necessary for transcription, our results indicate that the change in β-globin RNA occurred at a post-transcriptional level. In addition, we have shown that the 3'-untranslated region of HMG-CoA reductase cDNA imparted oxysterol-mediated post-transcriptional regulation to β-globin RNA, an effect that required protein synthesis.

L10 ANSWER 10 OF 19 CAPLUS © COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1995:387048 CAPLUS <<LOGINID::20060831>>
DOCUMENT NUMBER: 122:184726
TITLE: Type C Niemann-Pick disease fibroblasts and their transformed cell lines are hypersensitive to HMG-CoA reductase inhibitors
AUTHOR(S): Yamamoto, T.; Ohashi, T.; Tokoro, T.; Maekawa, K.; Eto, Y.
CORPORATE SOURCE: School of Medicine, Jikei University, Tokyo, 105, Japan
SOURCE: Journal of Inherited Metabolic Disease (1994), 17(6), 718-23
CODEN: JIMDDP; ISSN: 0141-8955
PUBLISHER: Kluwer
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The deficiency of exogenous cholesterol transport within fibroblasts of Niemann-Pick disease type C (NPC) has been addressed. In this report we confirmed that the endogenous synthesis of cholesterol within cells was markedly increased in NPC fibroblasts and those transformed by origin-defective simian virus 40. The transformed fibroblasts and those of the primary culture were hypersensitive to 3-hydroxy-3-methylglutaryl-CoA reductase inhibitors as a consequence of their dependence on endogenous cholesterol biosynthesis. The transformed fibroblasts should help further biochem. and genetic research in this

condition.

L10 ANSWER 11 OF 19 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1994:569833 CAPLUS <<LOGINID::20060831>>
DOCUMENT NUMBER: 121:169833
TITLE: Lovastatin inhibits HIV-1 expression in h9 human T lymphocytes cultured in cholesterol-poor medium
AUTHOR(S): Maziere, Jc; Landureau, Jc; Giral, P; Auclair, M; Fall, L; Lachgar, A; Achour, A; Zagury, D
CORPORATE SOURCE: Lab. Biochim., Fac. Med. Saint-Antoine, Paris, 75012, Fr.
SOURCE: Biomedicine & Pharmacotherapy (1994), 48(2), 63-7
CODEN: BIPHEX; ISSN: 0753-3322
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The effects of the HMG-CoA reductase inhibitor lovastatin on HIV-1 expression and sterol synthesis have been investigated in the human H9 lymphocytic cell line. To this purpose, sterol synthesis from 14C-acetate, cell multiplication and reverse transcriptase activity have been measured in parallel at various times after cell infection by HIV-1. It was found that nine days after viral loading, lovastatin inhibited both sterol synthesis and viral multiplication as assessed by the reverse transcriptase activity. Since HIV infection has been shown to induce alterations in membrane cholesterol content, suggesting that the virus cycle may be partially dependent upon cellular cholesterol, inhibitors of cholesterol synthesis could be useful in research on slowing down HIV propagation.

L10 ANSWER 12 OF 19 MEDLINE on STN
ACCESSION NUMBER: 2001114363 MEDLINE <<LOGINID::20060831>>
DOCUMENT NUMBER: PubMed ID: 11143546
TITLE: [Toxic liver damage caused by HMG-CoA reductase inhibitor].
Toxischer Leberschaden durch HMG-CoA-Reduktase-Hemmer.
AUTHOR: Heuer T; Gerards H; Pauw M; Gabbert H E; Reis H E
CORPORATE SOURCE: Medizinische Klinik I, Krankenhaus Maria Hilf, Monchengladbach.. theo.heuer@t-online.de
SOURCE: Medizinische Klinik (Munich, Germany : 1983), (2000 Nov 15) Vol. 95, No. 11, pp. 642-4.
Journal code: 8303501. ISSN: 0723-5003.
PUB. COUNTRY: Germany: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: German
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200102
ENTRY DATE: Entered STN: 22 Mar 2001
Last Updated on STN: 22 Mar 2001
Entered Medline: 15 Feb 2001
AB CASE REPORTS: We report on 4 patients who were referred to the clinic with suspected acute hepatitis and to investigate high transaminase values. After exclusion of specific hepatitis, unspecific virus hepatitis, autoimmune hepatitis, a metabolic disorder damaging the liver and extrahepatic cholestasis, a toxic liver damage remained as the probable cause and was histologically verified. Since other drugs and alcoholics could be eliminated as possible causes of the damage, the toxicity had to be attributed to statin ingestion. CLINICAL COURSE: After discontinuation of the medication with continuation of all other therapeutic agents of the general practitioners, the transaminase values normalized within a few weeks. Renewed administration of statin was not prescribed for ethical reasons. CONCLUSION: Therefore, when prescribing a HMG-CoA-reductase inhibitor, the possibility

of liver damage should be mentioned and regular checks of the transaminase values should be performed.

L10 ANSWER 13 OF 19 MEDLINE on STN
ACCESSION NUMBER: 87308417 MEDLINE <<LOGINID::20060831>>
DOCUMENT NUMBER: PubMed ID: 3040778
TITLE: The effect of factors released from the tumor-transformed cells on DNA synthesis, mitosis, and cellular enlargement in 3T3 fibroblasts.
AUTHOR: Dafgard E; Engstrom W; Larsson O; Zetterberg A
SOURCE: Journal of cellular physiology, (1987 Aug) Vol. 132, No. 2, pp. 295-302.
Journal code: 0050222. ISSN: 0021-9541.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198710
ENTRY DATE: Entered STN: 5 Mar 1990
Last Updated on STN: 5 Mar 1990
Entered Medline: 7 Oct 1987
AB Quiescent serum-starved 3T3 cells can be stimulated to initiate DNA synthesis after addition of conditioned media from spontaneously tumor-transformed 3T3 cells (3T6-cells) or from SV-40-transformed 3T3 cells (SV-3T3 cells). The conditioned media were found to stimulate both the chromosome cycle (i.e., DNA synthesis and cell division) and the growth cycle (i.e., cellular enlargement). Furthermore, addition of conditioned media to quiescent 3T3 cells increased the activity of HMG CoA reductase--an enzyme previously proposed to exercise some control on cell proliferation in 3T3 cells (Larsson and Zetterberg: J. Cell. Physiol. 129:99-102, 1986. The increased activity of HMG CoA reductase after treatment with tumor cell conditioned media was correlated to the stimulatory effects on DNA synthesis. By treating 3T3 cells stimulated to resume proliferation by addition of conditioned media with mevinolin (a competitive inhibitor of HMG CoA reductase) the activity of HMG CoA reductase as well as the DNA synthesis and cell division were efficiently inhibited. In contrast, HMG CoA activity was not coupled to the cellular enlargement. Therefore, it is proposed that one set of factors present in tumor cell conditioned media preferentially stimulates the chromosome cycle by increasing the HMG-CoA reductase activity, whereas another set of factors is responsible for growth in cell size. Both types of factors are required for balanced growth.

L10 ANSWER 14 OF 19 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2001:112085 BIOSIS <<LOGINID::20060831>>
DOCUMENT NUMBER: PREV200100112085
TITLE: HMG-CoA reductase inhibitors interfere with VEGF signaling in human endothelial cells.
AUTHOR(S): Kong, Dequan [Reprint author]; Park, Ho-Jin [Reprint author]; Tang, Dongjiang [Reprint author]; Galper, Jonas B. [Reprint author]
CORPORATE SOURCE: Brigham and Women's Hosp, Boston, MA, USA
SOURCE: Circulation, (October 31, 2000) Vol. 102, No. 18 Supplement, pp. II.64. print.
Meeting Info.: Abstracts from American Heart Association Scientific Sessions 2000. New Orleans, Louisiana, USA. November 12-15, 2000. American Heart Association.
CODEN: CIRCAZ. ISSN: 0009-7322.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English

isopentenyl diphosphate and other downstream products, including synthesis of sterol and nonsterol lipids and prenylation of proteins. A correlation was noted between higher intrinsic rates of mevalonate synthesis by a cell and susceptibility to inhibition by Fmev. Thus, sensitivity of a cell line to inhibition by Fmev was associated with markedly increased rates of HMG CoA reductase activity that were further increased by incubation with Fmev. Whereas Fmev depleted cellular levels of the prenylated protein Ras in the sensitive cell line U-937, there was no depletion of cellular Ras levels in the resistant cell line EL-4, but rather, there was a shift of Ras from membrane to cytosol, as expected for inhibition of prenylation. These results suggest that leukemic cells with increased HMG CoA reductase activity produce increased levels of an endogenous mevalonate-derived inhibitor that leads to Ras depletion and suppression of cell growth. As a result, inhibition of the growth of these transformed cells might be specifically accomplished by Fmev.

L10 ANSWER 19 OF 19 EMBASE

ACCESSION NUMBER: 2000243430 EMBASE <<LOGINID::20060831>>
TITLE: Compactin and simvastatin, but not pravastatin, induce sone morphogenetic protein-2 in human osteosarcoma cells.
AUTHOR: Sugiyama M.; Kodama T.; Konishi K.; Abe K.; Asami S.; Oikawa S.
CORPORATE SOURCE: S. Oikawa, Suntory Biomedical Research Limited, 1-I-1 Wakayamadai, Shimamoto-cho, Osaka 618-8503, Japan
SOURCE: Biochemical and Biophysical Research Communications, (19 May 2000) Vol. 271, No. 3, pp. 688-692. .
Refs: 30
ISSN: 0006-291X CODEN: BBRCA
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
030 Pharmacology
033 Orthopedic Surgery
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 27 Jul 2000
Last Updated on STN: 27 Jul 2000

AB Bone morphogenetic protein (BMP)-2, a member of the BMP family, plays an important role in osteoblast differentiation and bone formation. To discover small molecules that induce BMP-2, a luciferase reporter vector containing the 5'-flanking promoter region of the human BMP-2 gene was constructed and transfected into human osteosarcoma (HOS) cells. By the screening of an in-house natural product library with stably transfected HOS cells, a fungal metabolite, compactin, known as an inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, was isolated. The stimulation of the promoter activity by compactin seemed to be specific for BMP-2 gene in HOS cells, since it had little effect on BMP-4 or SV40 promoter activity and the stimulation was not observed in Chinese hamster ovary (CHO) cells. RT-PCR analysis and alkaline phosphatase assay revealed that compactin induced an increase in the expression of BMP-2 mRNA and protein. Like compactin, simvastatin also activated the BMP-2 promoter, whereas pravastatin did not. The statin-mediated activation of BMP-2 promoter was completely inhibited by the downstream metabolite of HMG-CoA reductase, mevalonate, indicating that the activation was a result of the inhibition of the enzyme. These results suggest that statins, if they are selectively targeted to bone, have beneficial effects in the treatment of osteoporosis or bone fracture. (C) 2000 Academic Press.

ENTRY DATE: Entered STN: 28 Feb 2001
Last Updated on STN: 15 Feb 2002

L10 ANSWER 15 OF 19 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2000:426449 BIOSIS <<LOGINID::20060831>>
DOCUMENT NUMBER: PREV200000426449
TITLE: Efficacy and tolerability of pravastatin for the treatment of HIV-1 protease inhibitor-associated hyperlipidaemia: A pilot study.
AUTHOR(S): Baldini, Francesco [Reprint author]; Di Giambenedetto, Simona [Reprint author]; Cingolani, Antonella [Reprint author]; Murri, Rita [Reprint author]; Ammassari, Adriana [Reprint author]; De Luca, Andrea [Reprint author]
CORPORATE SOURCE: Istituto di Clinica delle Malattie Infettive, Universita Cattolica del S. Cuore, Rome, Italy
SOURCE: AIDS (Hagerstown), (28 July, 2000) Vol. 14, No. 11, pp. 1660-1662. print.
CODEN: AIDSET. ISSN: 0269-9370.
DOCUMENT TYPE: Letter
LANGUAGE: English
ENTRY DATE: Entered STN: 4 Oct 2000
Last Updated on STN: 10 Jan 2002

L10 ANSWER 16 OF 19 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2000:322084 BIOSIS <<LOGINID::20060831>>
DOCUMENT NUMBER: PREV200000322084
TITLE: Defining patient risks from expanded preventive therapies.
AUTHOR(S): Tolman, Keith G. [Reprint author]
CORPORATE SOURCE: Gastroenterology/Liver Division, University of Utah School of Medicine, 50 North Medical Drive, Salt Lake City, UT, 84132, USA
SOURCE: American Journal of Cardiology, (June 22, 2000) Vol. 85, No. 12A, pp. 15E-19E. print.
CODEN: AJCDAG. ISSN: 0002-9149.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 26 Jul 2000
Last Updated on STN: 7 Jan 2002

AB In clinical trials, all lipid-lowering agents have been associated with mild, asymptomatic elevations of alanine aminotransferase (ALT) and asparate aminotransferase enzymes. This, along with the fact that 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors are hepatotoxic in some animals, led the US Food and Drug Administration (FDA) to recommend monitoring of liver enzymes for all lipid-lowering agents, except the bile acid sequestrants. Because the drugs act by different mechanisms, ALT elevations may be a pharmacodynamic effect related to lipid lowering, rather than a direct effect of the drug. Animal studies support this assumption. ALT elevations of 3 times the upper limit of normal occur in <3% of patients in clinical trials of lipid-lowering drugs. The elevations are transient and often dose-related, and they usually revert to normal while continuing therapy and have never been associated with hepatotoxicity. Confounding factors include alcohol, acetaminophen, and pre-existing liver disease, such as chronic hepatitis C and type II diabetes with fatty liver, which are both associated with mild, intermittent elevations of ALT. The more important issue is whether or not lipid-lowering agents are hepatotoxic. There are case reports of hepatotoxicity (cholestasis, jaundice, hepatitis, chronic active hepatitis, fatty liver, cirrhosis and acute liver failure) with all of the drugs, except cholestyramine. To date there are just 5 cases of documented liver failure linked to lovastatin. There is no evidence that monitoring reduces the rate of hepatotoxicity. Mild elevations of ALT that occur with many drugs,

including HMG-CoA reductase inhibitors, do not predict hepatotoxicity. Liver enzyme elevations appear to be a class characteristic of lipid-lowering agents. Hepatotoxicity is a rare idiosyncratic reaction, occurring only with sustained released nicotinic acid.

L10 ANSWER 17 OF 19 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

ACCESSION NUMBER: 1999:144548 BIOSIS <<LOGINID::20060831>>
DOCUMENT NUMBER: PREV199900144548
TITLE: Role of isoprenylation in the inhibitory action of lovastatin on proliferation of SV40 immortalized human saphenous vein smooth muscle cells.
AUTHOR(S): Unlu, Shebnem; Mason, Catherine D.; Hughes, Alun D.
CORPORATE SOURCE: Clin. Pharmacol., Natl. Heart Lung Inst., Imperial Coll. Sci. Technol. Med., St. Mary's Hosp., South Wharf Road, London W2 1NY, UK
SOURCE: Biochemical Society Transactions, (Nov., 1998) Vol. 26, No. 4, pp. S324. print.
Meeting Info.: 666th Meeting of the Biochemical Society. Sheffield, England, UK. July 29-31, 1998.
CODEN: BCSTB5. ISSN: 0300-5127.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 13 Apr 1999
Last Updated on STN: 13 Apr 1999

L10 ANSWER 18 OF 19 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

ACCESSION NUMBER: 1997:403743 BIOSIS <<LOGINID::20060831>>
DOCUMENT NUMBER: PREV199799709946
TITLE: Regulation of proliferation and Ras localization in transformed cells by products of mevalonate metabolism.
AUTHOR(S): Cuthbert, Jennifer A. [Reprint author]; Lipsky, Peter E.
CORPORATE SOURCE: Dep. Intern. Med., Univ. Texas Southwestern Med. Cent. at Dallas, Dallas, TX 75235-9151, USA
SOURCE: Cancer Research, (1997) Vol. 57, No. 16, pp. 3498-3505.
CODEN: CNREA8. ISSN: 0008-5472.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 24 Sep 1997
Last Updated on STN: 21 Nov 1997

AB Lovastatin, an inhibitor of 3-hydroxy-3-methylglutaryl (HMG) CoA reductase, and 6-fluoromevalonate (Fmev), an inhibitor of diphosphomevalonate decarboxylase, blocked the synthesis of downstream mevalonate products, including prenyl-derived lipids, and prevented membrane localization of Ras in the myeloid cell line U-937. In contrast to lovastatin, which induced cytosol localization of Ras in U-937 cells, Fmev failed to increase cytosolic Ras and also completely prevented the proliferation of U-937 cells. Growth of U-937 cells was restored by the addition of lovastatin to Fmev-blocked cells. These results implied that a product of mevalonate metabolism proximal to isopentenyl diphosphate was responsible for the suppression of proliferation. To delineate the action of this endogenous inhibitor of cell proliferation and determine the relationship between its impact on Ras localization and cell proliferation, the effect of Fmev on a variety of leukemia- and lymphoma-derived cells was examined. Whereas Fmev blocked the growth of these cell lines, there were more than 50-fold differences in the concentrations required to inhibit the growth of individual cell lines by 90%. Regardless of its effect on cell proliferation, the biochemical effect of Fmev was similar. Thus, Fmev uniformly prevented the conversion of radiolabeled mevalonate to